REMARKS/ARGUMENTS:

Claims 55-71 are pending in the application. Reexamination and reconsideration of the application, in view of the following remarks, are respectfully requested.

CLAIM REJECTIONS UNDER 35 U.S.C. §103:

Claims 55-71 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Applicants' admission on page 7 (first two full paragraphs) of Applicants' response of May 23, 2005, in view of Swayze et al., 6,316,626. The Applicant respectfully traverses this rejection.

Claim 55 is as follows:

> A device comprising a plurality of unmodified biopolymer and a solid support, wherein the solid support has at least one surface comprising pendant acyl fluoride functionalities, and wherein an unmodified end of the biopolymer is attached to the solid support by reaction with the pendant acyl fluoride functionalities, in the absence of a spacer arm.

Applicant respectfully submits that the combination of the Applicants' admission and Swayze cannot render claim 55 obvious, because the Applicants' admission and Swayze fail to teach or suggest a "device comprising a plurality of unmodified biopolymer ... wherein an unmodified end of the biopolymer is attached to the solid support by reaction with the pendant acyl fluoride functionalities, in the absence of a spacer arm."

The Examiner in the "Response to Arguments" at page 6 of the Office Action, acknowledges the Applicant's arguments, which are that a person of ordinary skill in the art would not think that biopolymers could be efficiently immobilized directly

on substrates without modification and without use of linkers and that if anyone had attempted to attach unmodified biopolymers to a solid support, such attempt was unsuccessful and was abandoned. The Examiner further acknowledges the Applicant's argument that the statement as a whole must be considered including portions that would lead away from the claimed invention.

Nevertheless, the Examiner believes the above arguments are not persuasive because "Applicant's statement nevertheless admits that the invention of attaching unmodified biopolymers to a solid support was known or used by others in this country before the invention by Applicant."

Again, the Applicant respectfully disagrees. In order to establish a *prima facie* case of obviousness, three basic criteria must be met:

> "First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP 2143

The Applicant respectfully submits that the Applicant's statement, that attempts to attach unmodified biopolymers without linkers were unsuccessful and abandoned, does not constitute a suggestion or motivation to try such an attachment. Therefore, the first criterion is not met.

The Applicant's admission indicates that attempts to attach unmodified biopolymers without linkers were unsuccessful and abandoned. Consequently, there is not a reasonable expectation of success and the second criterion is not met. Since the three basic criteria for obviousness have not been met, a *prima facie* case of obviousness has not been established.

Swayze has no teaching of immobilizing directly the biopolymers to a solid support, and was not relied on by the Examiner for such. Thus, in view of the foregoing, the Applicant respectfully submits that the Examiner has not met the burden of providing a *prima facie* case of obviousness.

In addition, the Applicant respectfully submits that Swayze fails to teach or suggest the use of acyl fluoride to functionalize a solid support to further attach a biopolymer.

The Examiner in the "Response to Arguments" at page 7 of the Office Action, states with respect to Swayze that,

> "the solid support has pendant acyl fluoride functionalities and the biopolymer is attached to the solid support by reaction with the pendant acyl fluoride functionalities, as claimed by the Applicant. Moreover, a scaffold itself is equivalent to a solid support and thus Swayze teaches using pendant acyl fluoride functionalities to attach a biopolymer to a sold support (see col. 108, lines 31-53)."

The Applicant respectfully disagrees. The solid supports of Swayze do <u>not</u> employ pendant acyl fluoride functionalities for the attachment of any moieties of any kind. The solid supports of Swayze are particles of controlled pore glass or any of a large variety of polymeric resins functionalized to carry any of a large variety of pendant reactive chemical groups (Swayze, column 35, lines 40-64). None of the listed groups represent acyl functionalities, much less acyl fluoride functionalities.

Even if the support-bound scaffolds, created as above, were to be viewed as "solid supports," there would still be no teaching or suggestion of acyl fluorides being used as means to attach any moiety of any kind. Instead, every instance of attachment to such loosely-construed "solid supports" either taught or suggested by Swayze occurs via reaction with a pendant diversity site (Swayze, column 14, line

63-column 15, line 33; column 17, lines 19-27). All such attachment reactions involve attack on an amine or hydroxyl pendant on the scaffold by a reactive group pendant on the moiety to be attached, referred to as a building block. In Swayze, the product of the reaction between an acyl fluoride and an amine is an amide linkage binding the support-bound scaffold to the building block which carried the acyl fluoride functionality (Swayze, column 27, lines 62-65).

In addition, Swayze fails to teach or suggest the attachment of biopolymers, either modified or unmodified, to solid supports by any means whatsoever. The only species taught by Swayze for attachment to actual solid supports are the scaffolds, which are not biopolymers. In the case of support-bound scaffolds, the only species taught by Swayze for attachment are building blocks. Building blocks, according to Swayze, are an extremely diverse class composed, primarily of small non-polymeric moieties Additionally they include compounds with alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, and heteroaryl carbon backbones, some of which, presumably, could be polymeric backbones, and they include some biologically derived moieties – e.g., amino acids. (Swayze, column 26, line 17-column 35, line 39). But the building block class does not include biopolymers.

Furthermore, the scaffolds of Swayze are not equivalent to solid supports. Swayze defines, for example, certain monocyclic and bicyclic amine compounds to be scaffolds (Swayze column 3, line 24-column 6, line 36; column 8, line 9-column 10, line 11). Scaffolds may be as small as 20 atoms (e.g., formula I, col. 3, lines 50-58, where $R_1 = CH_2$, $R_2 = R_3 = R_5 = R_6 = H$, $W = X = CH_2$, ms = mb = 1 and mc = md = 0). Since this is a freely soluble nanometer-scale molecule, it would not be classified as a solid support, or the equivalent of a solid support.

Lastly, since the composition of the scaffolds is so dissimilar to those of biopolymers, the chemical reactivities of the scaffolds would not be expected to

approximate those of biopolymers. A characteristic of biopolymers well known to those skilled in the art is their predisposition to fold spontaneously into three-dimensional conformations which may, and often do, "hide" functionalities of the biopolymer inside a matrix composed of the remainder of the biopolymer. This hiding or sequestering phenomenon renders these functionalities comparatively unavailable for reaction and is thought to be the principal cause of inefficient and/or unpredictable reactivity of these functionalities under chemical conditions where they would otherwise be expected to react efficiently and predictably.

In contrast, the scaffolds of Swayze, are intentionally designed with a degree of rigidity specifically to limit or preclude folding such as one would expect of biopolymers (Swayze, column 3, lines 4-10; column 17, lines 48-54). This resistance to folding and consequent prevention of sequestering is critical to maintaining the availability of the scaffold functionalities for the combinatorial reaction schemes envisioned by Swayze. The building blocks of Swayze are small molecules, dissolved in the reaction media suggested by Swayze. These small molecules are free to diffuse through the reaction media to encounter other reactants. It is well known to those of ordinary skill in the art that functionalities pendant upon solid supports exhibit very different reactivities than the same functionalities pendant upon dissolved species – typically greatly reduced reactivities as compared with those on dissolved species. Accordingly, reactions exhibited by acyl fluorides pendant upon building blocks are not particularly likely to occur with acyl fluorides pendant upon solid supports.

In summary, Swayze's use of acyl fluoride functionalities pendant upon building blocks to attach support-bound scaffolds to building blocks would not be considered by one of ordinary skill in the art to be a useful predictor of the utility of

acyl fluoride functionalities pendant upon solid supports for attaching biopolymers to solid supports.

In light of the foregoing, Applicant respectfully submits that the Applicant's admission and Swayze could not have rendered claim 55 obvious, because the combination of references fails to teach or suggest each and every claim limitation. Claims 56-71 depend from claim 55 and cannot be rendered obvious for at least the same reasons as claim 55. Withdrawal of these rejections is thus respectfully requested.

Claims 55-71 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Barany et al., 6,852,487 in view of Swayze et al., 6,316,626. The Applicant respectfully traverses this rejection.

Applicant respectfully submits that the Barany and Swayze cannot render claim 55 obvious, because the combination of references fails to teach or suggest a "device comprising a plurality of unmodified biopolymer ... wherein an unmodified end of the biopolymer is attached to the solid support by reaction with the pendant acyl fluoride functionalities, in the absence of a spacer arm."

The Examiner states,

> "Barany et al. discloses the invention substantially as claimed. More specifically, as to claim 55, Barany et al. discloses a plurality of biopolymer and a solid support (col 23, line 21), wherein the solid support has at least one surface comprising pendant acyl halide functionalities (col. 23, line 23), and wherein an unmodified end of the biopolymer is attached to the solid support by reaction with the pendant acyl halide functionalities in the absence of a spacer arm, (col. 26, lines 36-39, and col. 23, lines 20-23, disclosing the attachment of

pre-synthesized probes, and col. 32, lines 25-28, disclosing spotting of oligomers to a solid support.)"

The Applicant respectfully disagrees. The Examiner in the "Response to Arguments" at page 8 of the Office Action, cites column 26, lines 36-40 of Barany as teaching the attachment of unmodified probes.

Barany at column 26, lines 36-40 states,

> "To prepare the arrays of the present invention, the solid supports must be charged with DNA oligonucleotides or PNA oligomers. This is achieved either by attachment of pre-synthesized probes, or by direct assembly and side-chain deprotection (without release of the oligomer) onto the support."

Apparently, the Examiner is relying on the above two sentences which are devoid of any specific experimental detail to rebut the Applicant's arguments that Barany uses modified ends and linkers.

First of all, "pre-synthesized" probes do not mean that the probes are not modified. On the contrary, the teachings of Barany teach that the probes are modified.

For example, the Applicant submits that section of Barany (column 26, lines 7-23) that precedes the above excerpt teaches modified oligonucleotides.

> "DNA oligonucleotides can be synthesized and terminated with a residue of the amino acid tryptophan, and conjugated efficiently to supports that have been modified by tris(alkoxy)benzyl ester (hypersensitive acid labile ("HAL")) or tris(alkoxy)benzylamide ("PAL") linkers [F. Albericio, et al., J. Org. Chem., 55:3730-3743 (1990); F. Albericio and G. Barany, Tetrahdron Lett., 32:1015-1018 (1991)], which are hereby incorporated by reference). Other potentially rapid chemistries involve reaction of thiols with bromoacetyl or maleimido functions. In one variation, the terminus of amino functionalized DNA is modified by bromoacetic anhydride, and the bromoacetyl function is

captured by readily established thiol groups on the support. Alternatively, an N-acetyl, S-tritylcysteine residue coupled to the end of the probe provides, after cleavage and deprotection, a free thiol which can be captured by a maleimido group on the support. As shown in FIG. 12, chemically synthesized probes can be extended, on either end. Further variations of the proposed chemistries are readily envisaged. FIG. 12A shows that an amino group on the probe is modified by bromoacetic anhydride; the bromoacetyl function is captured by a thiol group on the support. Alternatively, an N-acetyl, S-tritylcysteine residue coupled to the end of the probe provides, after cleavage and deprotection, a free thiol which can be captured by a maleimido group on the support." (Barany, column 26, lines 7-23).

In addition, when Barany does include specific details for the attachment of biopolymers, the biopolymers used are either amino-modified oligonucleotides (column 45, lines 2-4; column 45, lines 10-15; column 49, lines 8-11; column 50, lines 19-21) or oligo-Trp-end-labelled DNA and PNA (column 28, lines 65-67; column 39, line 64).

Furthermore, when Barany, at column 5, lines 6-9, refers to the "attachment of previously assembled oligonucleotide probes to a solid support," a reference in which all such oligonucleotide probes were modified by incorporation of either a 3'- or a 5'-terminal amino modification is cited. This reference: Beattie et al., "Advances in Genosensor Research," Clin. Chem., 41(5) 700-706 (1995) is submitted concurrently herewith.

Therefore, based on the teachings of Barany, a person of ordinary skill in the art would be discouraged from attempting a linkage in the absence of modifying the biopolymer or without the use of a linker arm. Barany, as acknowledged by the Examiner, fails to teach the use of acyl fluorides and instead, the Examiner relies on Swayze for supplying this teaching. However, Swayze cannot remedy this defect for the reasons discussed above.

In light of the foregoing, Applicant respectfully submits that the cited references could not have rendered claim 55 obvious, because the combination of references fails to teach or suggest each and every claim limitation. Claims 56-71 depend from claim 55 and cannot be rendered obvious for at least the same reasons as claim 55. Withdrawal of these rejections is thus respectfully requested.

Applicant believes the foregoing amendments comply with requirements of form and thus may be admitted under 37 C.F.R. § 1.116(b). In addition, admission is requested under 37 C.F.R. § 1.116(b) as presenting rejected claims in better form for consideration on appeal.

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, in view of the foregoing remarks, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles, California telephone number (310) 785-4674 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,
HOGAN & HARTSON L.L.P.

Date: June 5, 2006

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